Approaching the patent cliff: how did we get here and what comes next

THOMSON REUTERS
Generics & API Intelligence

Kate Kuhrt
PharmaChem Outlook, DCAT Week
March 2011, New York

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Agenda

• Patent cliff
• Major forces impacting generics
• Generics’ response strategies
• Implications for API manufacturers
• Predictions for the future
About Thomson Reuters Generics & API Intelligence

- 20 years experience in tracking API manufacturing and generics
- An industry pioneer in research and analysis of global API manufacturing activity
- Develop and market the Newport database family
- More than 300 customers and 3,000 users across 43 countries in the Innovator, Generic, OTC and API manufacturing industries
- Serving the needs of
  - Business Development & Licensing Professionals
  - Portfolio Selection Teams
  - R&D and Regulatory Specialists
  - API Sourcing Specialists
- Team based in Portland, Maine, USA
Number of small molecules losing patent protection in the US

Source: Newport Premium™
2010 sales of small molecules losing patent or exclusivity protection in the US

Source: Newport Premium™

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How did we get here…

• Poor pipeline productivity
  – Significant R&D expenses not translating into increasing number of product launches

• Increasing regulation
  – Increased focus on safety
  – Increased focus on cost effectiveness
... and what comes next?
Major forces impacting generics in the short term

• Increasing competition
  – Emerging market players
  – Big pharma involvement with generics

• Near universal encouragement of brand to generic substitution
  – Cost containment by private and public payers

• Increased focus on biologics
Increasing competition: Total ANDA approvals

![Bar chart showing increasing competition for ANDA approvals over years 2005 to 2010. The chart indicates a growing trend in ANDA approvals and holders.](image-url)
Increasing competition:
Total ANDA approvals by Indian generics

Source: Newport Premium™
Increasing competition: US ANDAs belonging to Chinese companies

• Chinese ANDAs are a reality!
  – First final ANDA approval in December 2010 (Novast)

• 3 additional companies with final ANDAs acquired from companies like Ranbaxy, Par, Actavis
  – Zhejiang Huahai (Huahai US Inc)
  – Beijing Pharmaceutical (Beijing Double Crane)
  – Yabao Pharma Group (Beijing Yabao) (ANDAs discontinued)

• Additional filings waiting for approval

• FDA backlog slowing down manufacturing transfer to China
Increasing competition: Launch of Authorized Generics is a fact of life

Source: Newport Deals Module
Increasing competition:
Norvasc (amlodipine besylate)

% of Units Dispensed

Source: Newport Market Share Module

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Increasing competition: Authorized Generics deals

Source: Newport Deals Module
Emerging opportunities in follow-on biologics

• Biosimilar products have been approved in a number of regulated markets (EU, Australia, Japan, Canada)

• Finally have a pathway for abbreviated filings in the US
  – Still many uncertainties, including about exclusivity period
  – Not clear how many companies will use the abbreviated pathway
Follow-on biologics: Patent and exclusivity expiry for key products

Source: Newport Premium™
Follow-on biologics: 12 v. 7 year exclusivity expiry

$24b in 2010 sales

$12b in 2010 sales

Source: Newport Premium™
## Major generic companies active in FOB development

<table>
<thead>
<tr>
<th>Company</th>
<th>Proteins</th>
<th>Antibodies</th>
<th>Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teva</td>
<td>FP</td>
<td>UD</td>
<td>FP</td>
</tr>
<tr>
<td>Sandoz</td>
<td>FP</td>
<td>UD</td>
<td></td>
</tr>
<tr>
<td>Hospira</td>
<td>FP</td>
<td>UD</td>
<td></td>
</tr>
<tr>
<td>STADA</td>
<td>FP</td>
<td>UD</td>
<td></td>
</tr>
<tr>
<td>Actavis</td>
<td>FP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranbaxy</td>
<td>FP</td>
<td>UD</td>
<td>FP</td>
</tr>
<tr>
<td>Dr Reddy’s</td>
<td>FP</td>
<td>FP</td>
<td></td>
</tr>
<tr>
<td>Apotex</td>
<td>FP</td>
<td>UD</td>
<td>FP</td>
</tr>
<tr>
<td>Cipla</td>
<td></td>
<td>UD</td>
<td></td>
</tr>
</tbody>
</table>

**Key:** FP = Full Production, UD = Under Development

Source: TR Research
Big Pharma will also compete

**Merck** signaled its clear intent to get aggressive about the biosimilar business…

Fierce Biotech 2.09

**Pfizer** takes Biosimilars Plunge

PharmaTech Talk 10.10

**Amgen** is particularly interested in developing biosimilars for the Asian and Latin American markets

Fierce Biotech 1.11
Biotech capabilities among Indian companies

<table>
<thead>
<tr>
<th>Company</th>
<th>Protein</th>
<th>Antibody</th>
<th>Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocon</td>
<td>FP</td>
<td>FP</td>
<td></td>
</tr>
<tr>
<td>Shantha</td>
<td>FP</td>
<td>UD</td>
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</tr>
<tr>
<td>Intas</td>
<td>FP</td>
<td>UD</td>
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<tr>
<td>Panacea</td>
<td>UD</td>
<td></td>
<td>FP</td>
</tr>
<tr>
<td>Lupin</td>
<td>FP</td>
<td>UD</td>
<td></td>
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<tr>
<td>Zydus Cadila</td>
<td>FP</td>
<td>FP</td>
<td></td>
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<tr>
<td>Torrent</td>
<td>FP</td>
<td></td>
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<td>Wockhardt</td>
<td>FP</td>
<td>UD</td>
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<td>Glenmark</td>
<td>UD</td>
<td>UD</td>
<td>FP</td>
</tr>
<tr>
<td>Bharat</td>
<td>UD</td>
<td></td>
<td>FP</td>
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<tr>
<td>Avesthagen</td>
<td>UD</td>
<td></td>
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<tr>
<td>USV</td>
<td>UD</td>
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<td>Serum Institute</td>
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<td>UD</td>
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<tr>
<td>Reliance</td>
<td>UD</td>
<td>UD</td>
<td></td>
</tr>
</tbody>
</table>

Key: FP = Full Production, UD = Under Development
Generics’ response to opportunities and challenges

• Patent challenges
  – Get the maximum out of remaining small molecule opportunities

• Consolidation and Partnering
  – Economies of scale
  – Expansion into emerging markets
  – Expansion into niche and follow-on biologics
  – Access to API

• CRAMS and Innovation
Patent challenges: First Para IV certifications posted by FDA

Source: Newport Premium™
Patent challenges:
Products losing NCE exclusivity protection

Number of Products

Source: Newport Premium™
Patent challenges:
First Para IV patent certifications by dose form

Source: Newport Premium™

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Patent challenges: Paragraph IV filings by country

- USA
- India
- Israel
- Switzerland
- Canada
- Japan
- Germany
- Iceland
- Netherlands
- Others
Top Paragraph IV filers: cumulative number of products with patent challenge

Source: Newport Premium™
Consolidation and partnering

- Economies of scale
- Expansion into emerging markets
- Expansion into niche and follow-on biologics
- Access to API
Consolidation and partnering: M&A spend in the generic industry since 2003

Source: Newport Generic Deals Module

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Consolidation and partnering: Economies of scale

<table>
<thead>
<tr>
<th>Company</th>
<th>2001</th>
<th>Company</th>
<th>2010</th>
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</thead>
<tbody>
<tr>
<td>Teva</td>
<td></td>
<td>Teva</td>
<td></td>
</tr>
<tr>
<td>Sandoz</td>
<td></td>
<td>Sandoz</td>
<td></td>
</tr>
<tr>
<td>Barr</td>
<td></td>
<td>Mylan</td>
<td></td>
</tr>
<tr>
<td>Mylan</td>
<td></td>
<td>Hospira</td>
<td></td>
</tr>
<tr>
<td>IVAX</td>
<td></td>
<td>Watson</td>
<td></td>
</tr>
<tr>
<td>Merck KGaA</td>
<td></td>
<td>Perrigo</td>
<td></td>
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<tr>
<td>ratiopharm</td>
<td></td>
<td>STADA</td>
<td></td>
</tr>
<tr>
<td>Hexal</td>
<td></td>
<td>Sanofi</td>
<td></td>
</tr>
<tr>
<td>Watson</td>
<td></td>
<td>Actavis</td>
<td></td>
</tr>
<tr>
<td>Alpharma</td>
<td></td>
<td>Ranbaxy</td>
<td></td>
</tr>
</tbody>
</table>

Source: Newport Generic Deals Module

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Consolidation and partnering: Expansion into emerging markets

Teva – Lab Chile, Infarmasa
Sanofi – Medley, Kendrick
Pfizer – Teuto
Watson – Moksha8
Nycomed – Lab Farmacol

Stada – Makiz, Nizhpharm
Actavis – Zdorovje
Gedeon Richter – Akrihin
ICN – Marbiopharm
Sanofi – Bioton Wostok

Fresenius – Dabur
Daiichi – Ranbaxy
Mylan – Matrix
Watson – Sekhsaria
Abbott - Piramal

Source: Newport Generic Deals Module
## Consolidation and partnering: Expansion into niche products

<table>
<thead>
<tr>
<th>Company</th>
<th>Partner/Target</th>
<th>When</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akorn</td>
<td>Generamedix, Cipla</td>
<td>2008</td>
</tr>
<tr>
<td>Aspen</td>
<td>Strides, Onco Therapeutics</td>
<td>2007</td>
</tr>
<tr>
<td>Breckenridge</td>
<td>GenePharm</td>
<td>2009</td>
</tr>
<tr>
<td>Dabur</td>
<td>Combino Pharm</td>
<td>2007</td>
</tr>
<tr>
<td>Jubilant</td>
<td>Hollister</td>
<td>2007</td>
</tr>
<tr>
<td>Fresenius</td>
<td>Dabur, APP, Ribbon</td>
<td>2005-</td>
</tr>
<tr>
<td>Hospira</td>
<td>Mayne, Pliva, Fresenius, Orchid</td>
<td>2006-</td>
</tr>
<tr>
<td>Mylan</td>
<td>Bioniche</td>
<td>2010</td>
</tr>
<tr>
<td>Par</td>
<td>Mustafa</td>
<td>2005</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Claris, Aurobindo, Strides</td>
<td>2008-</td>
</tr>
<tr>
<td>Sagent</td>
<td>Strides, Itochu, Astral, Hisun</td>
<td>2007-</td>
</tr>
<tr>
<td>Sandoz</td>
<td>Sabex, Ebewe</td>
<td>2009</td>
</tr>
</tbody>
</table>

Source: Newport Generic Deals Module
Consolidation and partnering: First wave of biologic deals: EPO, G-CSF

- Hospira via STADA (2006)
- Barr via Pliva (2005)
- Lupin via Bharat (2006)
- Mayne via Pliva (2005)
- STADA via DSM Biologics (2001), Bioceuticals (2001)

Source: Newport Generic Deals Module
Consolidation and partnering:
2\textsuperscript{nd} wave of biologic deals

- Aceto & Three Rivers (2005)
- Merck & Avecia Biologics, Insmed (2007-)
- Mylan via Biocon (2009)
- Teva via CoGenesys (2008), Lonza (2009)
- STADA via Forum Biosciences (2007)
- Watson via Arrow/Eden Biodesign (2010)
- EGIS via Celltrion (2010)

Source: Newport Generic Deals Module
Consolidation and partnering: Backward integration

<table>
<thead>
<tr>
<th>Company</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teva</td>
<td>Barr (Pliva), IVAX, Sicor</td>
</tr>
<tr>
<td>Mylan</td>
<td>Matrix (Concord Biotech, Astrix, Mchem)</td>
</tr>
<tr>
<td>Hospira</td>
<td>Paclitaxel and filgrastim facilities</td>
</tr>
<tr>
<td>Watson</td>
<td>Sekhsaria</td>
</tr>
<tr>
<td>Perrigo</td>
<td>Agis (Chemagis)</td>
</tr>
<tr>
<td>Zentiva (Sanofi)</td>
<td>Slovakofarma, Leciva</td>
</tr>
<tr>
<td>Actavis</td>
<td>Sanmar, Fako, Zdravlje, Zhejiang Chiral Medicine</td>
</tr>
</tbody>
</table>

Source: Newport Generic Deals Module
World generic API manufacturing landscape

Experience in supplying regulated markets

- Established
- Less Established
- Potential Future
- Local

Source: Newport Premium™
Of the 450+ experienced manufacturers…

• ~1/3 are pure API players
• Almost 20% market generic finished dose in the US

Source: Newport Premium™
Of the 450+ experienced manufacturers…

• Close to 1/3 are located in India and China
Comparing Indian API manufacturer ratings, 2006 to 2010

Source: Newport Premium™
Comparing Chinese API manufacturer ratings, 2006 to 2010

Source: Newport Premium™
Comparing Italian API manufacturer ratings, 2006 to 2010

Source: Newport Premium™

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FDA inspections of API manufacturers

Source: Newport Premium™
European COS Filings

Source: Newport Premium™

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## Challenges in Indian and Chinese sourcing markets

<table>
<thead>
<tr>
<th>Cost Type</th>
<th>China</th>
<th>India</th>
<th>Europe</th>
<th>U.S.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labor</td>
<td>$</td>
<td>$</td>
<td>$$$</td>
<td>$$$</td>
</tr>
<tr>
<td>Environmental</td>
<td>$$$</td>
<td>$</td>
<td>$</td>
<td>$</td>
</tr>
<tr>
<td>Energy</td>
<td>$$</td>
<td>$$</td>
<td>$</td>
<td>$</td>
</tr>
<tr>
<td>IP Protection</td>
<td>$$</td>
<td>$$</td>
<td>$$</td>
<td>$$</td>
</tr>
<tr>
<td>cGMP Compliance and Monitoring</td>
<td>$$$</td>
<td>$$</td>
<td>$</td>
<td>$</td>
</tr>
</tbody>
</table>
CRAMS growth fueling Indian M&A activity…

<table>
<thead>
<tr>
<th>Company</th>
<th>Notable Deals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dishman</td>
<td>Synprotec, Carbogen, IO3S, Solvay Veenendaal</td>
</tr>
<tr>
<td>Aurobindo</td>
<td>Dayton NJ Facility, Milpharm UK, TAD Pharma</td>
</tr>
<tr>
<td>DRL</td>
<td>Quimicas Falcon, DowPharma, BASF Shreveport</td>
</tr>
<tr>
<td>Jubilant</td>
<td>PSI, Hollister-Stier, Draxis, Specialty Molecules</td>
</tr>
<tr>
<td>Orchid</td>
<td>Mano, Bexel</td>
</tr>
<tr>
<td>Piramal</td>
<td>Biosyntech, Pfizer Morpeth</td>
</tr>
<tr>
<td>Shasun</td>
<td>Rhodia CS, Polymerix Piscataway</td>
</tr>
<tr>
<td>Zydus</td>
<td>Alpharma France, Nippon Universal, Labs Combix</td>
</tr>
<tr>
<td>Biocon</td>
<td>Nobex, AxiCorp</td>
</tr>
<tr>
<td>Hikal</td>
<td>Marsing</td>
</tr>
<tr>
<td>Torrent</td>
<td>Heumann Pharma</td>
</tr>
</tbody>
</table>

Source: Company Reports, TR Research
… and collaboration with Big Pharma R&D

<table>
<thead>
<tr>
<th>Generic Company</th>
<th>Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biocon</td>
<td>Amylin, CIMAB, Invitrogen, Itraca</td>
</tr>
<tr>
<td>Jubilant</td>
<td>AZ, DiscoveRx, Endo, Lilly, Entelos</td>
</tr>
<tr>
<td>Glenmark</td>
<td>Forest, Lilly, Dyax, Medicis</td>
</tr>
<tr>
<td>Piramal</td>
<td>Pierre Fabre, Morvus, Merck, Napo</td>
</tr>
<tr>
<td>Dr Reddy’s</td>
<td>Antares</td>
</tr>
<tr>
<td>Orchid</td>
<td>Merck</td>
</tr>
<tr>
<td>Ranbaxy</td>
<td>Merck</td>
</tr>
<tr>
<td>Torrent</td>
<td>AZ</td>
</tr>
<tr>
<td>Zydus</td>
<td>Karo, Lilly</td>
</tr>
</tbody>
</table>

Source: Newport Generic Deals Module
Generics investing in innovation

Source: Thomson Reuters Pharma
API manufacturers investing in specialized capabilities

- **High Potency**
  - Lucrative targets for API manufacturers
  - Many companies investing (SAFC, Novasep)

- **Continuous Process & Separation**
  - Indian companies using enzymatic catalysts
  - More Asian companies investing in micro-reactor technology

- **Micronization**
  - Improves formulation and dissolution properties
  - Better bioavailability, less API needed
Indian Import Registrations

Source: Newport Premium™
Chinese Import Registrations

- All Others
- Japan
- Italy
- China
- India

Source: Newport Premium™
Korean DMF filings

Source: Newport Premium™
The next decade

- Continued intra-generic consolidation
- Opportunistic uptake of generics by Big Pharma
- M&A used to buy into next-tier emerging, growth-oriented markets
- Emergence of Big Pharma/Big Biotech as dominant force in biosimilars
- Increase of regulations in emerging markets
- Increase of API manufacturing costs in India and China
- Focus in regulated markets on niche products
Thank You!

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